

The Hypertension in the Very Elderly Trial – latest data

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Early trials in the field of hypertension focused on adults in their fifties and sixties. However, with the passage of time, a progressive effort has been made to expand the evidence base for treatment in older adults. 2008 saw publication of data from the Hypertension in the Very Elderly Trial which demonstrated significant mortality and morbidity benefits from antihypertensive therapy in octogenarians. More recently, additional data from this cohort has been published suggesting that appropriate anti-hypertensive therapy may lead to a reduction in incident cognitive impairment and fractures, whilst a 1 year open label extension of the main study confirmed many of the original trial findings. This review provides an overview of the Hypertension in the Very Elderly Trial whilst also discursively evaluating the latest data.

Introduction

The 1960s saw publication of landmark data demonstrating the benefits of anti-hypertensive therapy [1–3]. Over the next four decades the evidence base for the treatment of hypertension in older adults was progressively expanded, for example by the Hypertension Detection and Follow-up Program, European Working Party on High Blood Pressure in the Elderly (EWPHE), Systolic Hypertension in the Elderly Program, Medical Research Council trial of hypertension treatment in older adults and the Systolic Hypertension in Europe trial [4–9].

Despite this, a trend analysis from the EWPHE trial suggested that the treatment of hypertension might be less effective or even harmful to the very old (aged over 80 years) [10]. Although a subsequent meta-analysis of the seven clinical trials which included both octogenarian men and women demonstrated a 34% reduction in the risk of stroke, this benefit was offset by a non-significant, 6% increase (95% CI –5, 18, $P = 0.05$) in all-cause mortality [11]. Yet the authors of the meta-analysis noted that a single, randomized controlled trial demonstrating no benefit from anti-hypertensive therapy, in this cohort, would negate the apparent benefits seen across their meta-analysis [11].

Given this uncertainty, the Hypertension in the Very Elderly Trial (HYVET) was commissioned with an open label

pilot undertaken to determine trial feasibility [11, 12]. In the pilot study, 1283 subjects aged over 80 years, with a sustained blood pressure of 160–210/90–109 mmHg, were allocated to one of three treatment arms – a diuretic based regimen, an angiotensin converting enzyme inhibitor based regimen or no treatment. Active treatment was associated with a reduction in all (fatal and non-fatal) cerebrovascular events with a relative hazard rate (RHR) of 0.47 (95% CI 0.24, 0.91; $P = 0.02$). However there was a non-significant rise in all cause mortality (RHR 1.23, 95% CI 0.75, 2.01; $P = 0.42$) in keeping with the results of the earlier meta-analysis.

Main study findings

A double-blind placebo-controlled trial with recruitment centres in 13 countries, HYVET prospectively analyzed data from 3845 older adults. The initial inclusion criteria demanded both systolic and diastolic hypertension (SDH) (mean systolic BP 160–210 mmHg; mean diastolic BP 90–109 mmHg), off treatment, during a 2 month run in period. These criteria were relaxed 3 years into the trial, to allow for a diastolic BP of <110 mmHg. This enhanced recruitment rates and led to the inclusion of subjects with isolated systolic hypertension (ISH). Subjects were then randomized to one of two treatment arms, the thiazide like

diuretic, indapamide (sustained release, 1.5 mg) or a matching placebo. Adjunctive therapy, in the form of perindopril (2 or 4 mg) or a matching placebo was also made available to investigators, if required, in order that subjects reached the target BP of <150/<80 mmHg [13].

Active treatment decreased BP when compared with placebo (−15 mmHg/−6 mmHg). The investigators also observed a non-significant reduction in the primary outcome measure, stroke, (unadjusted hazard ratio (HR) 0.70, 95% CI 0.49, 1.01; $P = 0.06$) and in all-cause cardiovascular morbidity and mortality (unadjusted HR 0.77, 95% CI: 0.60, 1.01; $P = 0.06$). Whilst a statistically significant reduction in congestive cardiac failure was also observed (unadjusted HR 0.36, 95% CI 0.22, 0.58; $P < 0.001$), it was an unexpected significant reduction in the incidence of all-cause mortality (unadjusted HR 0.79; 95% CI 0.65, 0.95; $P = 0.02$), which led to early termination of the trial. Moreover, active treatment was well tolerated. At 2 years there were no significant changes in serum potassium, uric acid, glucose and creatinine between the trial arms [13]. In fact, 448 serious adverse events (SAEs) were observed post-randomization in the placebo group. This contrasted with 358 SAEs in those receiving active therapy ($P = 0.001$) [13]. Furthermore, standing and seated BPs post-treatment were equivalent, suggesting that antihypertensive therapy was not associated with orthostatic hypotension [13].

These results undoubtedly provide evidence that anti-hypertensive therapy with sustained release indapamide \pm perindopril, in octogenarians, is beneficial. However, HYVET has its limitations. Having recruited large numbers of patients from Eastern Europe and China, the authors were criticized for not appreciating the increased prevalence of cerebrovascular events in these populations, when compared with adults from Western Europe – a factor which may exaggerate the potential benefit arising from active therapy [14]. In addition, it was notable that four centres closed in the first year due to data quality issues [13]. Equally, at the time of the second interim analysis (July 2007) the relative risk of all stroke (fatal and non-fatal) amongst those receiving active treatment was 0.59 (95% CI 0.40, 0.88; $P = 0.009$) when compared with placebo [13]. However, at the time of the final intention-to-treat analysis in October 2007, this significant reduction in the primary outcome measure failed to show statistical significance – the reasons for which have never been elaborated.

HYVET also has a number of methodological issues, namely the protocol amendment which provided for the inclusion of subjects with ISH and the variable methods for measuring blood pressure. Initially blood pressures were recorded with either a mercury sphygmomanometer or a validated automated device, but at the end of the trial a validated automated device was used in the majority of centres [13]. Full titration of active treatment resulted in 62% of SDH ($n = 174$) participants achieving target SBP by 2 years compared with 71% of those with ISH ($n = 124$).

Unsurprisingly, the corresponding results for DBP control were 40% ($n = 112$) and 78% ($n = 136$), respectively [15]. Given the log linear relationship between systolic blood pressure and clinical outcomes, the mortality and morbidity benefits seen in the trial might be a feature of systolic BP control, particularly in ISH, as opposed to achieved systolic and diastolic blood pressure.

In common with many other clinical trials in older people, the inclusion criteria also required that subjects be in relatively good physical and mental health (individuals with dementia and those resident in nursing homes were excluded), questioning the applicability of the trial outcomes to the real life setting [13, 16]. The number of subjects who smoked cigarettes (2.2% of females were current smokers and 13.0% of men), drank alcohol (34.5% of men and 6.8% of women) or had experienced a previous cardiovascular event (14.6% of men and 9.9% of women) was low. Although waist circumference was not reported, hypertensive status was infrequently associated with other features of the metabolic syndrome in the trial population, aside from those subjects who had suffered a prior cardiovascular event [17]. More importantly, the early evidence of mortality benefit resulted in a relatively short duration of follow-up (median 1.8 years) [13]. As a result, it remains unclear whether such benefits persist or diminish over a longer time course and although the inclusion criteria allowed for the enrolment of patients aged between 80 and 105 years, most were 80 to 85 years old (mean age; 83.6 years). Thus, the benefit of treatment above 85–90 years of age remains uncertain [18, 19].

Latest data

Earlier this year, results from a 1 year open label active treatment extension of HYVET were published. Trial participants receiving double-blind treatment at their final visit within the main study were deemed eligible for inclusion. However, those who had reached either primary or secondary end points during the main trial (apart from myocardial infarction, heart failure and skeletal fracture) were excluded. Comparing patients previously treated with active drug ($n = 924$; 54%) and those previously receiving placebo ($n = 788$; 46%), no significant differences were seen for stroke ($n = 13$; HR 1.92, 95% CI 0.59, 6.22; $P = 0.28$) or cardiovascular events ($n = 25$; HR 0.78, 95% CI 0.36, 1.72; $P = 0.55$), in keeping with the main study. Again, differences were seen for all-cause mortality (47 deaths; HR 0.48, 95% CI 0.26, 0.87; $P = 0.02$) [20]. Whilst these results strengthen the case for early benefit arising from anti-hypertensive therapy in octogenarians, the selective exclusion criteria are questionable.

When commissioning HYVET the trialists organized an inter-current sub-study to determine whether indapamide (\pm perindopril) reduced fracture rates in hypertensive older adults. This hypothesis, that indapamide (a thiazide-like diuretic) reduces urinary calcium excretion and as a result may reduce fracture rates, was tested in a sub-study.

When analyzing the 90 incident, validated fractures (38 in the active group; 52 in the placebo group) and adjusting for baseline risk factors, a HR of 0.58 was achieved (95% CI 0.33, 1.00; $P = 0.0498$). Allowing for all fractures, regardless of whether they were incident, validated fractures or not, resulted in an adjusted HR of 0.54 (95% CI: 0.32, 0.94; $P = 0.028$), suggesting that anti-hypertensive therapy in this cohort of patients, with a thiazide-like diuretic and an ACE inhibitor, does not increase and may decrease fracture rates [21]. Once again, the relative well being of the trial participants limits the potential applicability of these data to the general population. Furthermore, a failure to routinely identify vertebral fractures and difficulties in data collection may be sources of error.

The trial steering group also published an analysis evaluating the association of depression with cardiovascular mortality and morbidity, all-cause mortality and incident dementia. Having assessed depression at baseline and then annually using the Geriatric Depression Scale (GDS), the authors demonstrated a strong association between baseline GDS of ≥ 6 , all cause mortality and (fatal and non-fatal) cardiovascular endpoints over 2 years, with HRs of 1.78 (95% CI 1.40, 2.27; $P < 0.001$), 2.10 (95% CI 1.50, 2.96; $P < 0.001$) and 1.59 (95% CI 1.21, 2.09; $P < 0.001$), respectively [22]. Whilst each additional GDS point at baseline also increased these risks, the study was not designed to evaluate this association. Thus, social and economic status were not adequately controlled for and reverse causality could not be excluded.

As part of HYVET a baseline and annual assessment of cognitive function, the mini-mental state examination (MMSE), was undertaken. Having excluded subjects with a clinical diagnosis of dementia from participation, possible cases of incident dementia (MMSE score falling to < 24 points or a drop of ≥ 3 points in 1 year) were assessed by standard diagnostic criteria and expert review [23]. In multivariate analyses extremes of body habitus were associated with an increased risk of incident dementia – BMI < 18.5 (HR 1.90, 95% CI 1.06, 3.39; $P < 0.05$); BMI > 30 (HR 1.84, 95% CI 1.24, 2.72; $P < 0.01$), as was piracetam use (HR 2.72, 95% CI 1.60, 4.63; $P < 0.01$). Formal education was protective (HR 0.59, 95% CI 0.45, 0.78; $P < 0.01$), but no association was found with smoking status, alcohol consumption or gender. This may reflect the relative physical well being of the trial population [24]. Whilst the mean change in MMSE score at 2 years was -1.1 points (SD: 3.9) in the placebo group and $+0.7$ points (SD 4.0) in the treatment group ($P = 0.08$), the rates of incident all-cause dementia were 38/1000 patient-years in the placebo group and 33/1000 patient-years in the treatment group. Thus, no significant difference was observed between the two trial arms (HR 0.86, 95% CI 0.67, 1.09; P value not given). Further analysis of those experiencing a non-specified fall in MMSE score to < 24 or a decline of ≥ 3 points in 1 year yielded a similar non-significant result (HR 0.93, 95% CI 0.82, 1.05; P value not given) [23].

However using these data, a dynamic model of cognition that allowed all outcomes (cognitive worsening, stability, improvement or death) to be categorized simultaneously was developed. This appeared to detect small differences between the two trial arms, in favour of treatment. Although the model requires further validation, it suggests that cognitive change in those aged over 80 years is small, depends on baseline cognitive function and the relative efficacy of anti-hypertensive treatment [25].

Conclusion

HYVET demonstrated that anti-hypertensive therapy with indapamide (\pm perindopril) reduces all-cause mortality in octogenarians. This treatment regimen was also found to be associated with a large and significant reduction in heart failure, whilst proving particularly efficacious in the management of isolated systolic hypertension. A recently reported, 1 year, open label extension of HYVET also demonstrated significant all-cause and cardiovascular mortality benefits for those receiving active treatment, whilst secondary analyses indicate that exposure to indapamide \pm perindopril is associated with possible protection from incident fractures and dementia amongst this cohort.

Conflict of interest statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and that between 2001 and 2003 S.H.D. Jackson received speaker fees from Servier as a PROGRESS investigator.

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